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EXAMINER	
MACFARLANE, STACEY NEE	
ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,579	FRANCIS ET AL.	
	Examiner	Art Unit	
	STACEY MACFARLANE	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,13,19,34,43-45,55,61,76,85-87,97,103,106 and 119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,13,19,34,43-45,55,61,76,85-87,97,103,106 and 119* is/are rejected.

7)☒ Claim(s) *34 and 76* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/18/2006;3/21/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, in so far as they are drawn to a method comprising administering a hybrid protein comprising a therapeutic molecule wherein the therapeutic molecule is a protein, and the species of "insulin-like growth factors (IGF-1, IGF-2)" and amyotrophic lateral sclerosis, in the reply filed on September 4, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-3, 13, 19, 34, 43-45, 55, 61, 76, 85-87, 97, 103, 106 and 119, in so far as they read upon the elected invention, are under examination in the instant office action.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the

requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/408577, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The disclosure of the '577 provisional application fails to provide guidance or direction to one of ordinary skill in the art as to how to make a hybrid protein comprising IGF-1 or IGF2 and tetanus toxin fragment C (TTC), nor does the disclosure provide enabling support as to how to use administration of the hybrid protein as a method for treating a neurological disorder. Page 8 of the disclosure of the provisional '577 merely lists IGF-1 and IGF-2 as growth factors with which TTC can be used to enhance delivery. Table 1 (page 9) does not identify IGF-1 or IGF-2 as a preferred embodiment and fails to provide guidance as to how a hybrid of IGF and TTC is made. Furthermore, the working example provided provides only support for the making and use of a hybrid protein comprising superoxide dismutase and tetanus toxin fragment C (SOD:TTC). Therefore, Claims 3, 13, 19, 34, 45, 55, 61, 76, 85-87, 97, 103, 106 and 119 of the instant application are denied the benefit of the filing date of the provisional application and claims

Claim Objections

3. Claims 2, 3, 44, 45, 86, 87 and 106 are objected to for recitation of non-elected subject matter.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 19 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 19 and 61 are vague and indefinite in their recitation of a method comprising administering a hybrid protein into the cerebrospinal fluid or directly into the brain or spinal cord parenchyma, “wherein the hybrid protein is administered to at least about 10% of brain volume”. The volume of the cerebrospinal fluid is not equivalent to “at least about 10% brain volume”, and therefore the relationship between administration into the cerebrospinal fluid, as in the parent claim, and administration to at least about 10% brain volume are unclear. It is not known if the method is intending to recite "delivery" to at least 10% brain volume.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 1, 2, 13, 34, 43, 44, 55 and 76 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al. US Patent 5,780,024, issued July 14, 1998.

8. Claim 1 is drawn to a method for administering a therapeutic molecule to a subject comprising providing a hybrid protein comprising the therapeutic molecule and tetanus toxin fragment C (TTC), and administering the hybrid protein by infusion into the cerebrospinal fluid or directly into the brain or spinal cord parenchyma. Dependent Claims 2, 13, 34, 43, 44, 55 and 76 recite wherein the therapeutic molecule is a protein or peptide; wherein the mode of administration is intracerebroventricular administration or intrathecal infusion; wherein the hybrid protein is administered directly into the brain or spinal cord parenchyma by injection or infusion.

9. The Brown et al. '024 Patent teaches methods for administering a therapeutic molecule comprising providing a hybrid protein, comprising a therapeutic protein or peptide and TTC, and administering said hybrid protein by infusion into the cerebrospinal fluid or directly into the brain or spinal cord parenchyma. Specifically, the '024 Patent teaches a hybrid protein comprising the protein superoxide dismutase (SOD) and TTC and states the practice of the invention is that the hybrid protein is administered by a parenteral route, e.g. intrathecal or intracerebral ventricular, but that the preferable route of administration is directly into the CNS. The Patent teaches that this mode is most preferable because the CNS is shielded from the mammalian immune system, thereby administration directly to the CNS eliminates an immune reaction to tetanus, which most humans have been previously immunized against (column 4, lines 44-62). Therefore, the method of the invention fails to distinguish over that of the prior art and Claims 1, 2, 13, 34, 43, 44, 55 and 76 are rejected.

10. Claims 3, 45, 85-87 and 106 are rejected under 35 U.S.C. 102(a) as being anticipated by Chian et al., Program No. 413.14, Abstract Viewer/Itinerary Planner, Society for Neuroscience, August 2003, as evidenced by Fishman and Carrigan, Brain Research, 406(1-2):275-279, March 17, 1987 and Miana-Mena et al., *PNAS,* 99(5):3234-3239, March 5, 2002.

11. Claims 3, 45, 85-87 and 106 are drawn to a method for administering a therapeutic molecule to a subject, or specifically to a region that is not accessible via retrograde or transsynaptic transport from motor neurons, comprising providing a hybrid protein to a subject comprising providing a hybrid protein comprising the therapeutic molecule and tetanus toxin fragment C and administering the hybrid protein by infusion of the hybrid protein into the cerebrospinal fluid, or directly into the brain or spinal cord parenchyma; wherein the therapeutic molecule is a protein or peptide, wherein the protein is the instantly-elected IGF-1 and IGF-2; or a method for treating a neurological disorder comprising administering to a subject an effective amount of a hybrid protein comprising tetanus toxin fragment C and a therapeutic molecule by infusion of the hybrid protein into the cerebrospinal fluid or directly into the brain or spinal cord parenchyma; wherein the therapeutic molecule is a protein or peptide, specifically the instantly-elected IGF-1 and IGF-2; and wherein the neurological disorder is the instantly-elected amyotrophic lateral sclerosis.

12. The Chian et al. prior art teaches that IGF-1 is known in the art to have neurotrophic effects on motor neurons and to protect motor neuron from injury and disease in experimental animals in vivo. The reference states, however, “the efficacy of

IGF-1 for treating amyotrophic lateral sclerosis (ALS) may have been blunted by its poor penetration into brain and spinal cord due to the blood-brain barrier. To facilitate deliver of IGF-1 to the CNS, we have recombinantly linked human IGF-1 to the non-toxic C fragment of tetanus toxin (TTC)." The reference concludes by stating that bioavailability and neuroprotective activity of IGF-1:TTC hybrid protein are being evaluated by methods comprising administration "in rat CNS in vivo".

13. The Fishman and Carrigan reference is relied upon to demonstrate that it was well-known in the art, prior to filing, that intramuscular injection of TTC or TTC-linked hybrid proteins leads to transsynaptic transport from the muscle to the innervating motor neuron and retrograde delivery of TTC along the neuronal axon to the cell body of the neuron. The Miana-Mena reference is relied upon as evidence that from muscular injection, transsynaptic transport continues through neuron-to-neuron synaptic connections into the brainstem of the CNS.

14. The Chian et al. reference describes a method comprising providing a hybrid IGF-1:TTC protein and administering the hybrid protein directly into the brain or spinal cord, which comprise the CNS, by bypassing the blood-brain barrier. The method as disclosed by Chian et al. teaches administration to "a region of a subject's brain and spinal cord that is not accessible via retrograde or transsynaptic transport", as required by the claims. The reference also teaches methods of treating the instantly-elected neurological disorder of amyotrophic lateral sclerosis (ALS) comprising administration of the IGF-1:TTC hybrid protein. Therefore, the method of the claims fails to distinguish over that disclosed within the prior art.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

17. Claims 1-3, 13, 34, 43-45, 55, 76, 85-87, 97, 103, 106 and 119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al., US Patent 5,780,024 as applied to claims 1, 2, 13, 34, 43, 44, 55 and 76 above, and further in view of Kaspar et al., Science, 301:839-842, August 8 , 2003.

The Brown et al. '024 Patent teaches methods for administering a therapeutic molecule comprising providing a hybrid protein, comprising a therapeutic protein or peptide and TTC, and that said hybrid proteins can be either administered retrogradely (column 4, lines 34-43) or by infusion into the cerebrospinal fluid or directly into the brain or spinal cord parenchyma via parenteral route (intrathecal or intracerebral ventricular) or directly into the CNS (column 4, lines 44-62).

The '024 Patent does not teach a hybrid protein comprising the instantly-elected IGF-1 and TTC, nor does the Patent contemplate methods of treating ALS comprising administration of the specific IGF:TTC hybrid protein. The Kaspar et al. prior art, however, teaches that in vivo retrograde delivery of IGF-1 was known in the art to treat a mouse model for ALS.

It would have been obvious to one of ordinary skill in the art to combine the methods comprising providing and administering hybrid proteins as taught by Brown et al. with the IGF-1 as taught by Kaspar et al. A skilled artisan would be motivated to combine because the Kaspar reference demonstrates that IGF-1 successfully treats ALS in vivo upon retrograde transport, and the Brown method provides a means (coupling to TTC) by which molecules can be retrogradely or directly administered to the CNS. Based on the guidance and direction within each of the prior art references, such combination would have been well within the technical grasp of a skilled artisan. Furthermore, since each of the elements in combination are merely performing the same function as they did separately, then one of ordinary skill in the art would have been able to predictably combine the elements with a reasonable expectation of success. Therefore, the invention as a whole is *prima facie obvious*, if not actually anticipated by the reference.

Double Patenting

18. Applicant is advised that should claims 1 and 43 be found allowable, claims 34 and 76 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof.

When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

19. No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is (571)270-3057. The examiner can normally be reached on M,W and ALT F 7 am to 3:30, T & R 5:30 -5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stacey MacFarlane
Examiner
Art Unit 1649

/Jeffrey Stucker/
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